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HBM 2014- Educational Course:
Brain Stimulation: Past, Present and Future
Session on Modelling and imaging of the brain effects of stimulation: Combining TMS/PET
OBJECTIVES

- To describe different PET radiotracers used to image the dopaminergic system.
- To learn about the effects of brain stimulation on the dopaminergic system.
- To describe TMS effects on brain functions and diseases.
Dopamine

Learning

Reward

Executive function

Motor

Parkinson’s disease
Depression
Schizophrenia
Drug/Behavioral addiction

Huntington’s disease
Cortical-Striatal Connection

Cortex
- Frontal cort.
- Parietal cort.
- Temp. cort.

Striatum
- Caudate
- Putamen

Caudate → GPe
GPe → STN
STN → Gpi/SNr

Gpi/SNr → Thalamus
Thalamus → Cerebral Cortex

Corticostriatal Excitatory and Inhibitory Connections

Excitation
Inhibition
Dopamine modulation

Mink. Prog. Neurobiol., 1996
Mink. Arch. Neurol., 2003
Dopaminergic ligands: Pre-synaptic Imaging

- Tyrosine
- L-DOPA
- Dopamine
- VMAT
- DAT
- Receptors

**Pre-synaptic Imaging**

**Normal VMAT2 (DTBZ)**

**Normal DAT (MP)**

**Normal Striatal Uptake**

**FDOPA PET Scanning**
Dopamine D2/D3 Receptor Imaging Agent in Striatum

$[{^{11}}C]\text{raclopride}$

- PET agent
- Affinity (KD) = 1.1nM

$[{^{123}}I]\text{IBZM}$

- SPECT agent
- Affinity (KD) = 0.4nM

Jucaite et al., 2005

Laruelle et al., 1997

Laruelle et al., 1997
Post-synaptic Imaging in PD

Tyrosine → L-DOPA → Dopamine → VMAT → low receptor → high receptor → radio-tracer

DDC

Dopamine

D2/D3-R agonist

D2/D3-R antagonist

[^11C]PHNO

[^11C]Raclopride

25% 10% 38% 27%

DAT
Displacement Studies: Release of dopamine

Control condition

VS

Active condition

Classical Occupancy Model

- Depleted
- Baseline
- Stimulated

- Receptor
- Injected radioligand
- Neurotransmitter
Effects of Electrical Stimulation of Prefrontal Cortex on Dopamine Release

Taber and Fibiger, J of Neuroscience, 1995
rTMS Effect on Dopamine Release

Dorsal Striatum

Dopamine Levels (% baseline)

- rTMS
- Sham

Keck et al., Neuropharmacology, 2002
rTMS Effect on Dopamine Release

Dorsal Striatum


microdialysis experiments

Kanno et al. J. Neurol Sci. 2004
Neuro-receptor Imaging
rTMS & Striatal Dopamine

Macaque Monkeys

Ohnishi et al., 2004
TMS and $^{11}$C raclopride PET

Primary motor cortex

$X= -31, Y= -22, Z=52$

$X= -56, Y= -58, Z=-3$

dorsolateral PFC

$X= -40, Y= 32, Z=30$

$X= -56, Y= -58, Z=-3$

Strafella et al., 2003

Strafella et al., 2001
rTMS & Striatal Dopamine
- Stimulation of DLPFC -

Mean Δ%BP = -7.3%

Strafella et al., J of Neuroscience, 2001

Yeterian and Pandya
J. Comp. Neurol. 1991
rTMS & Striatal Dopamine
-Stimulation of motor cortex-

Mean $\Delta %BP = -9.5\%$

Strafella et al., Brain, 2003

Takada et al., Exp Brain Res. 1998
**Striatal dopaminergic effects**

**TMS versus amphetamine challenge**

**Figure:** Mean specific striatal IBZM-binding (striatal-occipital/occipital) before and after rTMS (left) and d-amphetamine (right) challenge.

Pogarell et al., Psychiatry Res, 2007
rTMS effect on behaviors and possible clinical relevance.
TMS-induced release of dopamine in PD

Reductions $[^{11}C]$ raclopride BP

- Reduction in $[^{11}C]$ BP in ipsilateral putamen
- 12.9 % reduction in asymptomatic hemisphere
- 9.45 % reduction in symptomatic hemisphere

Strafella et al., EJN 2005
Reduction $^{11}$C raclopride BP

- 61.4% increase in cluster size

Strafella et al., EJN 2005
Loss of functional segregation

Normal                  Nigrostriatal degeneration

• Because of loss of re-uptake sites, released dopamine diffuses out to more distant regions of the receptor population in the dopamine-denervated striatum > loss of functional segregation

Zigmond et al. TINS 1990
Functional implications for models of basal ganglia function in PD

- The neuroanatomical arrangement of the cortico-striatal system in a center-surround inhibitory pattern is thought to facilitate activity in cortico-striatal loops involved in the current task with concomitant suppression of competing motor networks.

- The loss of functional segregation may favor the de-arrangement of the selective facilitation/surround inhibition pattern leading to impaired inhibition of competing motor patterns.

Reduction of $[^{123}\text{I}]-\text{IBZM}$ binding following left prefrontal rTMS in major depression

B. Change of striatal $[^{123}\text{I}]-\text{IBZM}$-binding after rTMS

Pogarell et al. *J Psychiatr Res* 2006
Tyrosine $\rightarrow$ L-DOPA $\rightarrow$ DOPA $\rightarrow$ Dopamine $\rightarrow$ VMAT $\rightarrow$ DAT

- Tyrosine
- L-DOPA
- DOPA
- Dopamine
- VMAT
- DAT

- [¹¹C]Raclopride
- [¹¹C]FLB 457

- dopamine
- low receptor
- high receptor
- radio-tracer

- D2 antagonist

- 25%
- 38%
- 27%
Dopamine D2/D3 Receptor Imaging
Agent in Extrastriatal Region

- $[^{11}\text{C}]\text{FLB 457}$: PET agent, Affinity (Kd) = 20pM
- $[^{18}\text{F}]\text{Fallypride}$: PET agent, Affinity (Kd) = 33pM
- $[^{123}\text{I}]\text{Epidepride}$: SPECT agent, Affinity (Kd) = 24pM

References:
- Vilkman et al., 2007
- Riccardi et al., 2006
- Varrone et al., 2000
## Effect of Amphetamine on DA

Baboon monkey n=7
[^18F]Fallypride

<table>
<thead>
<tr>
<th>Region</th>
<th>Con.</th>
<th>Post-AMP</th>
<th>Δ%BP</th>
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<tbody>
<tr>
<td>striatum</td>
<td>22.36</td>
<td>11.31</td>
<td>-49</td>
</tr>
<tr>
<td>thalamus</td>
<td>1.51</td>
<td>1.14</td>
<td>-25</td>
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<tr>
<td>midbrain</td>
<td>0.91</td>
<td>0.65</td>
<td>-28</td>
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<tr>
<td>cingulate</td>
<td>0.31</td>
<td>0.18</td>
<td>-41</td>
</tr>
<tr>
<td>hippocampus</td>
<td>1.33</td>
<td>0.84</td>
<td>-36</td>
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*Slifstein et al., Synapse, 2004*
Effect of DLPFC rTMS on extrastriatal areas: \([^{11}\text{C}]\text{FLB457 PET Study}\)

**Target Area (DLPFC)**

- \(X=+/- 40, y=32, Z=30\)

- MagStim Rapid\(^2/8\)-shape coil
- Total stimulation block: 5 blocks
- Total stimulation pulse: 750 pulse
  - 15 1s 10Hz (100% RMT)
  - 10 sec inter train interval

- Siemens Biograph HiRez XVI PET/CT scanner
- 30 frames

Cho and Strafella 2009
Decrease of Cortical $[^{11}\text{C}]\text{FLB 457 BP}$ following Left DLPFC rTMS

$P < 0.001, k=20$

Cho and Strafella 2009
Decrease of Cortical $[^{11}\text{C}]\text{FLB 457 BP}$ following the Left DLPFC rTMS

-Individual BP in peak area-

* $P < 0.0001$

Cho and Strafella 2009
$[^{11}\text{C}]$FLB 457 BP after the **Left** DLPFC rTMS

<table>
<thead>
<tr>
<th>Control cond.</th>
<th>Active cond.</th>
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<tbody>
<tr>
<td>0.00</td>
<td>0.20</td>
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<tr>
<td>0.40</td>
<td>0.60</td>
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<tr>
<td>0.80</td>
<td>1.00</td>
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<tr>
<td>1.20</td>
<td>1.40</td>
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$[^{11}\text{C}]$FLB 457 BP after the **Right** DLPFC rTMS

<table>
<thead>
<tr>
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<th>Active cond.</th>
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<tbody>
<tr>
<td>0.00</td>
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<td>0.80</td>
<td>1.00</td>
</tr>
<tr>
<td>1.20</td>
<td>1.40</td>
</tr>
</tbody>
</table>

* $P < 0.0001$

**Left ACC**

**Right ACC**

Cho and Strafella 2009
Neural networks (Functional neuroanatomical/Neurochemical)

Prefrontal cortex
- Orbitofrontal cortex
- Medial prefrontal cortex
- Dorsolateral prefrontal cortex
- Anterior cingulate cortex

Striatum
- Ventral
- Dorsal

Cognition/Emotion
- Self control
- Impulsivity
- Decision making
  - Attention
  - Working memory
  - Planning
  - Reasoning
  - Prediction

Problem solving

Drug addiction
OCD
Gambling
Obesity
ADHD
Choice of hypothetical amount of money

**Smaller immediate** or **larger delayed**

- Total 150 trials
- Randomize for each test
- Range of K value: 0.5 ~ 0.0007
- Delay duration: 1 week ~ 10 years
Post-synaptic Imaging in PD

Tyrosine → L-DOPA → DDC → Dopamine → VMAT → [11C]PHNO

Dopamine

- low receptor
- high receptor
- radio-tracer

D2/D3-R agonist

D2/D3-R antagonist

[11C]Raclopride

[11C]PHNO

25% 10% 38% 27%
Reward prediction and brain activation

Tanaka et al., 2004
Stimulation Paradigm

MePFC (x=0, y=59, z=12)

Vertex (x=0, y=0, z=85)

Block 1
2min 35sec
150 pulses/Block

1sec
10sec

Cho et al., under review
CT scan & PET scan

Mask setting/IV root
Target mapping

rTMS
(VTX vs MePFC)

CT scan & PET scan

0 30 60 90 120 180

[11C]-(+)-PHNO bolus injection

Imaging study protocol

Cho et al., under review
rTMS of Medial Prefrontal Cortex on Delay Discounting Task

Cho et al., under review
-[^{11}C]-(+)-PHNO - DA release-

Caudate
Putaman
Globus pallidus

FDR corrected < 0.5, k = 100 voxel

Cho et al., under review
Reward prediction and brain activation

Tanaka et al., 2004
Implications